

REMARKS / ARGUMENTS

Reconsideration of the above-identified application respectfully requested.

The Present Invention

The present invention describes an improved commercial process for the production of carotenoid-cyclodextrin complexes and formulation of the complex for human ingestion. The carotenoids selected include, *inter alia*, lutein, lycopene, meso-zeaxanthin, and a mixture of lutein:zeaxanthin. The cyclodextrins selected from among natural cyclodextrins and their derivatives such as, for example, α -, β -, γ -cyclodextrin, and HP- β -cyclodextrin.

The present invention is based on the unexpected discovery that the commercial method of drying and formulation impacts the ability to retain the high bioavailability of lutein from a lutein-cyclodextrin complex. One of the inventive bioavailable forms is a freeze-dried lutein/ γ -cyclodextrin complex formulated in lecithin-vegetable oil or vegetable oil for soft gelatin capsules to be used in the nutritional supplement and pharmaceutical industry. The inventive freeze-dried complex shows a highly significant uptake *in vitro* in Caco2 intestinal cells as compared to, for example, a spray-dried complex described in U.S. Patent Application 10/309,999. The complex on formulation shows a significant uptake *in vitro* in the same model based on the excipients used in formulation.

The present invention also is based on the unexpected discovery that the process can be adapted with modifications to other carotenoids, including, *inter alia*, lycopene and mixtures of carotenoids, such as, for example, lutein and zeaxanthin, and to other cyclodextrins such as, for example, α -, β -, γ -, and hydroxypropyl β -cyclodextrins (HP- β).

The present invention also is based on the unexpected discovery that the *in vitro* uptake of lutein and zeaxanthin from the α -cyclodextrin complex is comparable to the γ -cyclodextrin complex neat.

The invention also discloses simultaneous uptake of stereoisomers lutein and zeaxanthin from cyclodextrin complexes.

The present invention, then, is a method for making a bioavailable carotenoid-cyclodextrin complex for animal ingestion. This method includes commercial production of the complex and formulating the complex for soft gelatin capsules to retain the properties of the complex. The preferred animal is a human with the route of administration being oral ingestion. The form of the complex for ingestion is a soft gelatin capsule, which may contain other ingredients, both active and inactive. *In vivo*, in a human study, the lutein/ γ -cyclodextrin complex improved the absorption of lutein as compared to a commercially available free lutein-oil formulation.

The Claim Rejections

A. Claims 1-10

Claims 1-10 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger (U.S. Patent No. 5,221,735), Fukamachi (U.S. Patent No. 4,929,774), Patel (U.S. Patent No. 6,569,463), and Orthoefer (U.S. Patent No. 4,125,630).

1. Claims 1-3

The Examiner cites Leuenberger as teaching a bioavailable, spray-dried cyclodextrin-carotenoid complex; but not teaching freeze-drying the cyclodextrin-carotenoid complex, not teaching the use of carotenoids other than lycopene and apocarotenol, not teaching the use of a specific oil, not teaching the oils of claim 3, and not using lutein or zeaxanthin of claim 6.

Fukamachi is cited as not teaching freeze-drying of formulations, but does teach the use of lutein and zeaxanthin in formulations and the use of edible oils.

Orthoefer is cited as teaching edible triglyceride oils.

2. Claim 4

Patel is cited as teaching lecithin, as recited in claim 4. This is combined with Leuenberger/Fukamachi/Orthoefer, as cited above.

3. Claims 5, 7, 8, and 10

Leuenberger/Fukamachi are cited, as above. Patel is further cited as teaching the use of cyclodextrin derivatives, the use of carotenes (lycopene and lutein), lecithin:vegetable oil ratios as in the claims, and soft gelatin capsules.

4. Claim 6

Leuenberger/Fukamachi/Patel are cited as above. Patel is noted as not teaching zeaxanthin, but Fukamachi does.

5. Claim 9

Leuenberger/Fukamachi are cited as above, with the notation that soft gelatin capsules are not taught. Patel is seen as supplying such teaching.

B. Claims 11-20

Claims 11-20 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger, Fukamachi, Patel, and Orthoefer.

1. Claims 11-13

Leuenberger, Fukamachi, Patel, and Orthoefer are cited as discussed above.

2. Claim 14

Leuenberger and Fukamachi are cited as above. They do not teach a formulation with a surfactant. Patel is cited as teaching the use of a surfactant, such as lecithin.

3. Claims 15, 17, 18, and 20

Leuenberger and Fukamachi are cited as above. Patel is cited as using cyclodextrin derivatives, the use of carotenes (lycopene and lutein), lecithin:vegetable oil ratios as in the claims, and soft gelatin capsules.

4. Claim 16

Leuenberger and Fukamachi are cited as above. Patel is cited as using cyclodextrin derivatives and the use of carotenes (lycopene and lutein), but not zeaxanthin. Fukamachi, however, does teach zeaxanthin.

5. Claim 19

Leuenberger and Fukamachi are cited as above, but do not teach formulations for human ingestion. Patel, however, does teach formulations for human ingestion.

The Cited Art

1. Leuenberger

Leuenberger proposes to make a water-soluble inclusion complex of apocarotenal and lycopene with cyclodextrin. The inclusion complex is made generally by dissolving cyclodextrin in water (or other polar solvent) and adding to a organic solvent solution of apocarotenal or lycopene. Organic solvents for the carotenoid include lower alkyl alcohols. (see generally col. 1, l. 60 bridging col. 2, l. 64). The weight ratio of apocarotenal and lycopene to cyclodextrin "is preferably about 1:10 to about 1:20". (col. 2, ll. 42-44). Separation of the organic solvent from the inclusion complex includes "[D]istillation and other methods of solvent removal...known in the art." (col. 2, ll. 51-42).

At this point in the discussion, the Examiner's attention is respectfully directed to the Rule 132 Declaration of Dr. Madhavi. Dr. Madhavi's credentials in the carotenoid field are impeccable. She is a co-inventor of the invention and co-applicant for the above-identified application. With respect to Leuenberger, Dr. Madhavi recites in ¶ 7 that the art has recognized the unpredictability of and difference in properties of inclusion complexes of different cyclodextrin with specific pharmaceuticals and natural compounds. Thus, when forming cyclodextrin complexes in general, the skilled artisan cannot predict with certainty the properties of the resulting complex.

Dr. Madhavi continues that carotenoids and apocarotenoids have varying structures and chemical properties. The number of carbon atoms, ring versus open chain structure, stereoisomers, hydrophobicity, *etc.*, are but a few of such recognized general differences.

Moreover, because of changes in structure and hydrophobicity, the carotenoids in general show different affinities towards cyclodextrins

As examples of such complex differences, Dr. Madhavi recites that even within the same class, for example xanthophylls, lutein and zeaxanthin are stereoisomers, which may have different affinities for a cyclodextrin. Lockwood (1996) has also been reported that complexation of astaxanthin, another xanthophyll, with sulfobutyl ether beta-cyclodextrin does not improve the solubility to result in a pharmaceutically acceptable chemical delivery system for humans. Also, complexation with cyclodextrins often may not result in increased bioavailability. For example, according to Spirichev *et al.* (1996) uptake of β -carotene from a cyclodextrin complex was lower as compared to the commercial oil dispersions or microencapsulated beadlets in human studies.

Dr. Madhavi concludes, then, that it is not obvious from the teachings of the art cited against the claims that different carotenoids can be complexed with the natural cyclodextrins or their derivatives or that complexation in general improves bioavailability. It also is not obvious that a mixture of stereoisomers can be complexed in a manner resulting in simultaneous uptake of the isomers into the cells. Further such teachings do not indicate the variability in uptake based on the cyclodextrins, a factor important for feasibility of commercial production and application of the complex.

It is beyond peradventure that Leuenberger falls woefully short of rendering the claims unpatentable.

2. Fukamachi

Fukamachi proposes to stabilize oxidation-sensitive compounds (vitamins, carotenoids, vitamin A acid, lemon oil—col. 3, ll. 45-58) against oxidation with a fat (triglyceride—col. 2, ll. 11-24), a complexing agent (phytic acid, phosphoric acid a polyphosphoric acid, sequestering agents—col. 2, ll. 25-243), and a coating agent (gelatin, casein, polysaccharide, alginate—col. 2, ll. 46-55). No cyclodextrins are shown in Fukamachi. To recover a solid product the dispersion can be subjected to “freeze drying, vacuum drying, spray drying or convection drying” (col. 3, ll. 26-31). Unfortunately, no freeze drying is used in any of the working examples—only the other drying methods recited.

In the first instance, Applicants question the use of Fukamachi in forming a rejection, since it is totally devoid of forming any complex in general and no cyclodextrin complexes in particular. With the art recognized lack of predictability of cyclodextrin/carotenoid complexes, what motivation was there for the Examiner to select Fukamachi? Applicants see none, but for

the impermissible use of hindsight. Fukamachi adds nothing of vitality to an already weak Leuenberger citation.

3. Orthoefer

Orthoefer proposes vegetable proteins for use as extenders or textured vegetable proteins in meat analogs. The Examiner cites Orthoefer as teaching edible triglyceride oils. For such proposition, Applicants have no disagreement. As for Orthoefer itself, it shows no carotenoids, no cyclodextrins, no carotenoid/cyclodextrin complexes, improving bioavailability of any substance, *etc.* Again, selection of Orthoefer to be held against the claims seems again to have come from impermissible hindsight. That is, the Examiner looks at the invention and then finds any catch-as-catch can reference that includes any ingredient recited in the claims.

4. Patel

Patel proposes to provide solid pharmaceutical compositions of a solid carrier and encapsulation coating. The coating can include pharmaceutical active agents, hydrophilic surfactants, hydrophobic surfactants, and triglycerides. Alternatively, the solid carrier can include the pharmaceutical active agents, hydrophilic surfactants, hydrophobic surfactants, and triglycerides. Processing includes any known technique (see col. 4, ll. 9-19).

Pharmaceutical active ingredients include, *inter alia*, carotenes, lutein, lycopene from a list that spans some 5 columns. Columns of surfactants and coating agents also are shown. Among the "solubilizers" are cyclodextrins from a list that spans over a column of listed solubilizer agents.

No cyclodextrin complexes appear to be shown in general much less carotenoid/cyclodextrin complexes. Again, considering the art recognized lack of predictability in the properties of such complexes, Patel is seen as adding nothing. Again, the Examiner seems to have selected references based on laundry lists of ingredients, rather than based on teachings vis-à-vis the invention.

5. Combination of Leuenberger, Fukamachi, Patel, and Orthoefer

With respect to the inclusion of a vegetable oil and the freeze-drying of the complex, Leuenberger describes use of oil to dissolve/disperse carotenoids followed by emulsification with water. Fukamachi describes use of vegetable oils in microencapsulation formulations for oxidation sensitive compounds and mentions lutein and zeaxanthin. However, the oils are used for making an emulsion with the gelatin matrix, an application entirely different from using the oil as an excipient or filler for the cyclodextrin complex, as in the present invention. Orthoefer

teaches using triglycerides as plasticizers for making meat analogs from vegetable proteins, again an application entirely different from formulating a carotenoid-cyclodextrin complex into a dosage form as in the present invention. Patel teaches the use of surfactants in the formulation. Again, it is not obvious from these teachings whether a carotenoid cyclodextrin complex can be formulated with these excipients without any adverse effects on the stability of the complex or the bioavailability.

Dr. Madhavi's declaration speaks to this issue also. She notes that the weak cyclodextrin/carotenoid bonds can be disrupted by a number of factors, including, *inter alia*, excipients used in formulations, including, *inter alia*, vegetable oils, medium chain triglycerides, and synthetic surfactants such as polysorbates, polyethylene glycols, and phospholipids such as lecithin. She continues that excipients with different polarities may interact with cyclodextrins resulting in the dissociation of the complex, inhibit the release of the actives, or modulate the dissolution properties. The interactions in general are often unpredictable in her expert opinion. Dr. Madhavi cites several publications on the interactions of cyclodextrin inclusion complexes of pharmaceuticals and flavor compounds with formulation excipients.

Again, the art combination structured in the claims rejections do not provide the certainty in teaching regarding the vegetable oil portion of the inventive product and process insofar as expected stability of the complex is concerned. The art, then, falls far short of rendering unpatentable the present invention.

With respect to the drying method used in forming the complex, Dr. Madhavi emphasizes the data reported in the working examples in the above-identified application. She states that the invention describes a commercially efficient process, which includes freeze-drying an aqueous dispersion of carotenoid-cyclodextrin complex. Freeze-drying was found to be efficient as compared to spray-drying with a 95% recovery of the product, as compared to 50% loss with spray-drying. Further, to her surprise, the freeze-dried product was superior to spray dried product in bioavailability studies. This unexpectedness is not dispelled or compromised just because freeze-drying is known in the art. The unexpectedness is that for Applicants' product only freeze-drying provided improved bioavailability for the product. Such unexpectedness testifies to the part of the invention and cannot be predicted.

Dealing with the soft gel issue, Dr. Madhavi notes that it is well known in the art that hydrophobic compounds present delivery challenges because of their physicochemical properties and soft gelatin capsules may offer a delivery system. However, complexation of carotenoids with cyclodextrins in general resulted in a hydrophilic, water dispersible fine powder. Such complexes are used for making directly compressible tablets or incorporated in to hard gelatin capsules, as cyclodextrins are expected to stabilize sensitive compounds against

degradation. However, Dr. Madhavi and her co-inventor found that complexation with cyclodextrins did not stabilize the carotenoids to afford the necessary commercially accepted shelf life in tablets or hard capsules. The soft-gelatin formulation was developed to stabilize the carotenoids. Again, this cannot be predicted and is unexpected.

Dr. Madhavi further states that when hydrophobic excipients, such as vegetable oils, are used, they may inhibit the dispersion of the complex in water; thus, reducing the uptake of the active molecule. However, to her surprise, she found that the complex retained its properties even after formulation with vegetable oil or vegetable oil-lecithin as excipients.

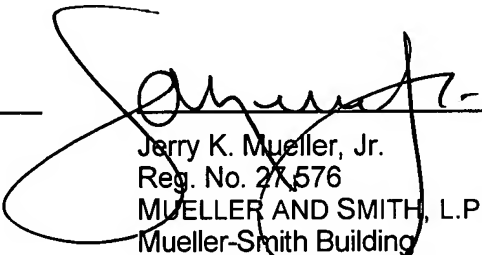
Dr. Madhavi concludes that in her opinion, it was totally unexpected that a commercially feasible, practical, and commercially viable process resulted for making a bioavailable cyclodextrin/carotenoid complex by freeze-drying a cyclodextrin/carotenoid complex in a molar ratio of between about 0.5:1 and 10:1, and adding such freeze-dried complex to a vegetable oil. The art cited simply does not render obvious the present invention in her expert opinion.

6. Summary

in view of the remarks, Rule 132 Declaration, and art submitted herewith, allowance of all claims and passage to issue of this application respectfully is requested.

Respectfully submitted,

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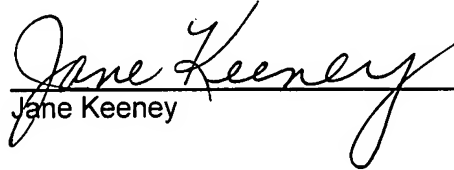
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